U.S. FOOD & DRUG ADMINISTRATION

Heparin Case Study

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Securing Medical Product Quality Through the Supply Chain
USP
March 29, 2017

Agenda

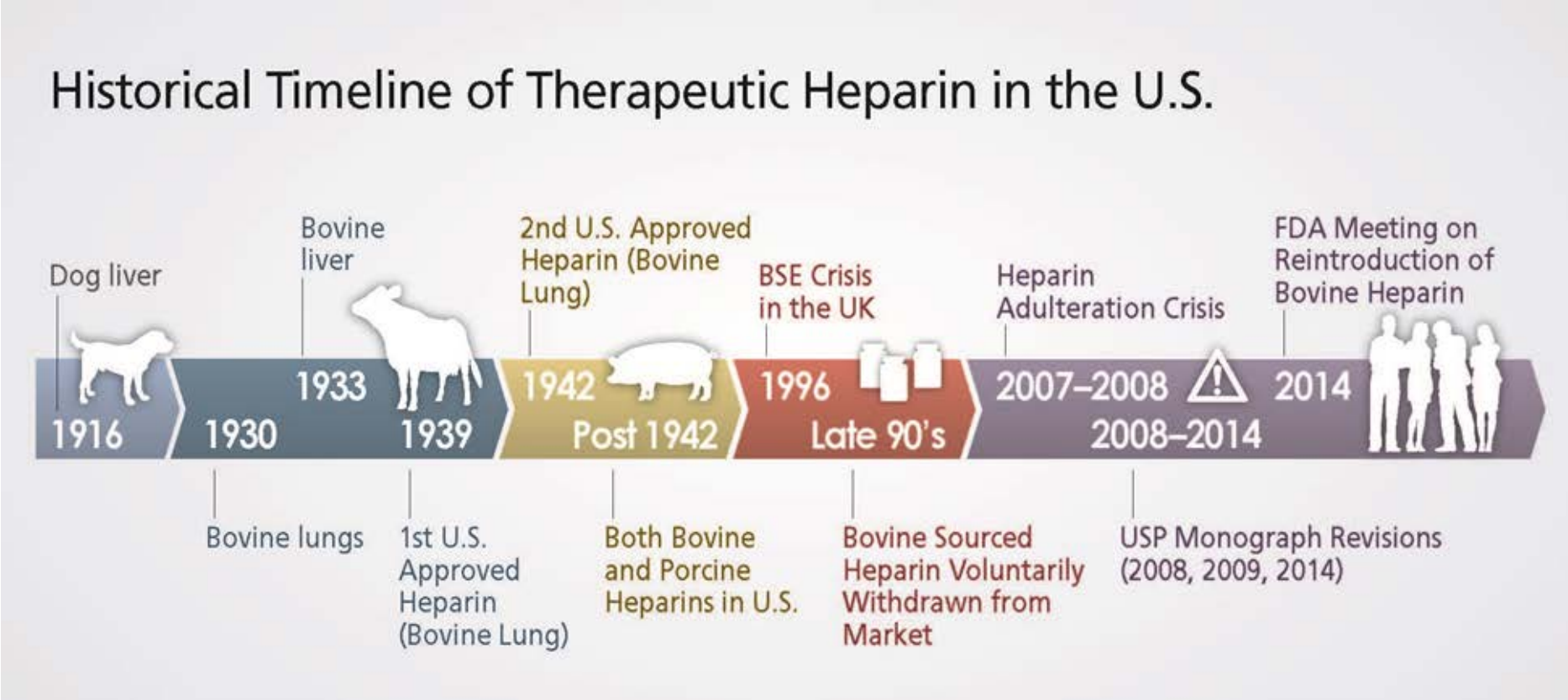
- Heparin Primer/History
- Supply Chain Characteristics
- Economically-Motivated Adulteration
- Blue Ear Disease
- OSCS
- What Happened
- FDA and USP Response
- Import Alert 55-03 and FDA Guidance
- Questions

Primer

- Heparin is a widely-used anticoagulant
- Used as a drug and incorporated in devices
- Derived naturally from porcine (pig) intestines
- Is a polymer, and variants exists (low vs. high molecular weights)

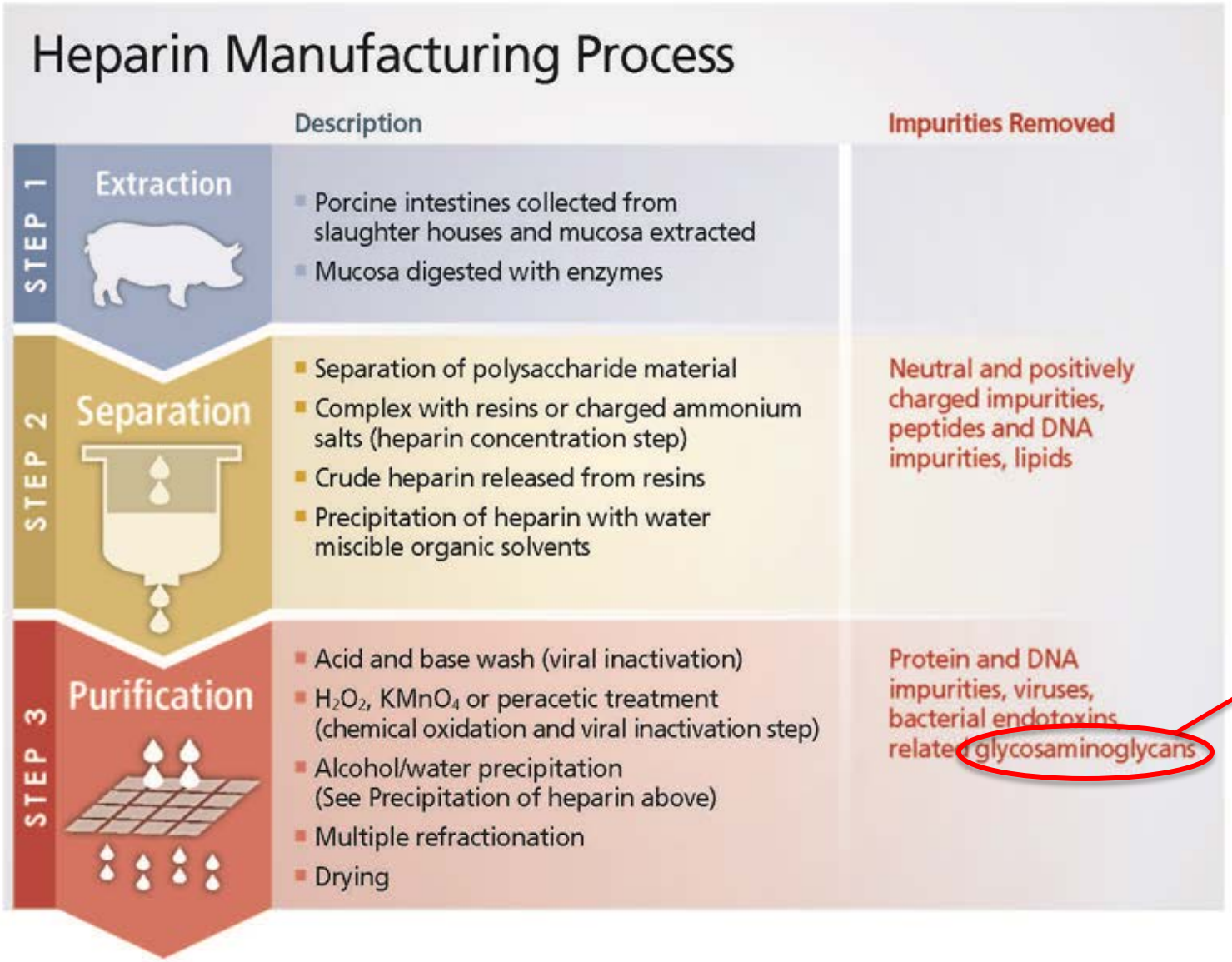
3

Heparin History



Keire DA, Mulloy B, Chase C, Al-Hakim A, Cairatti D, Gray E, Hogwood E, Morris T, A.S. Mourão P, da Luz Carvalho Soares M, and Szajek A. *"Diversifying the Global Heparin Supply Chain: Reintroduction of Bovine Heparin in the United States?"* Pharmaceutical Technology, 39(11), November (2015).

Heparin Manufacturing Process



Remember this

Keire DA, Mulloy B, Chase C, Al-Hakim A, Cairatti D, Gray E, Hogwood E, Morris T, A.S. Mourão P, da Luz Carvalho Soares M, and Szajek A. *"Diversifying the Global Heparin Supply Chain: Reintroduction of Bovine Heparin in the United States?"* Pharmaceutical Technology, 39(11), November (2015).

Supply Chain Characteristics

- It takes many animals to produce the heparin supply
  - ~3000 pigs for 1 kg of heparin
- The supply chain spreads back to slaughterhouses, crude manufacturers, and consolidators
- The supply chain is intertwined; it is an older industry with multiple manufacturers

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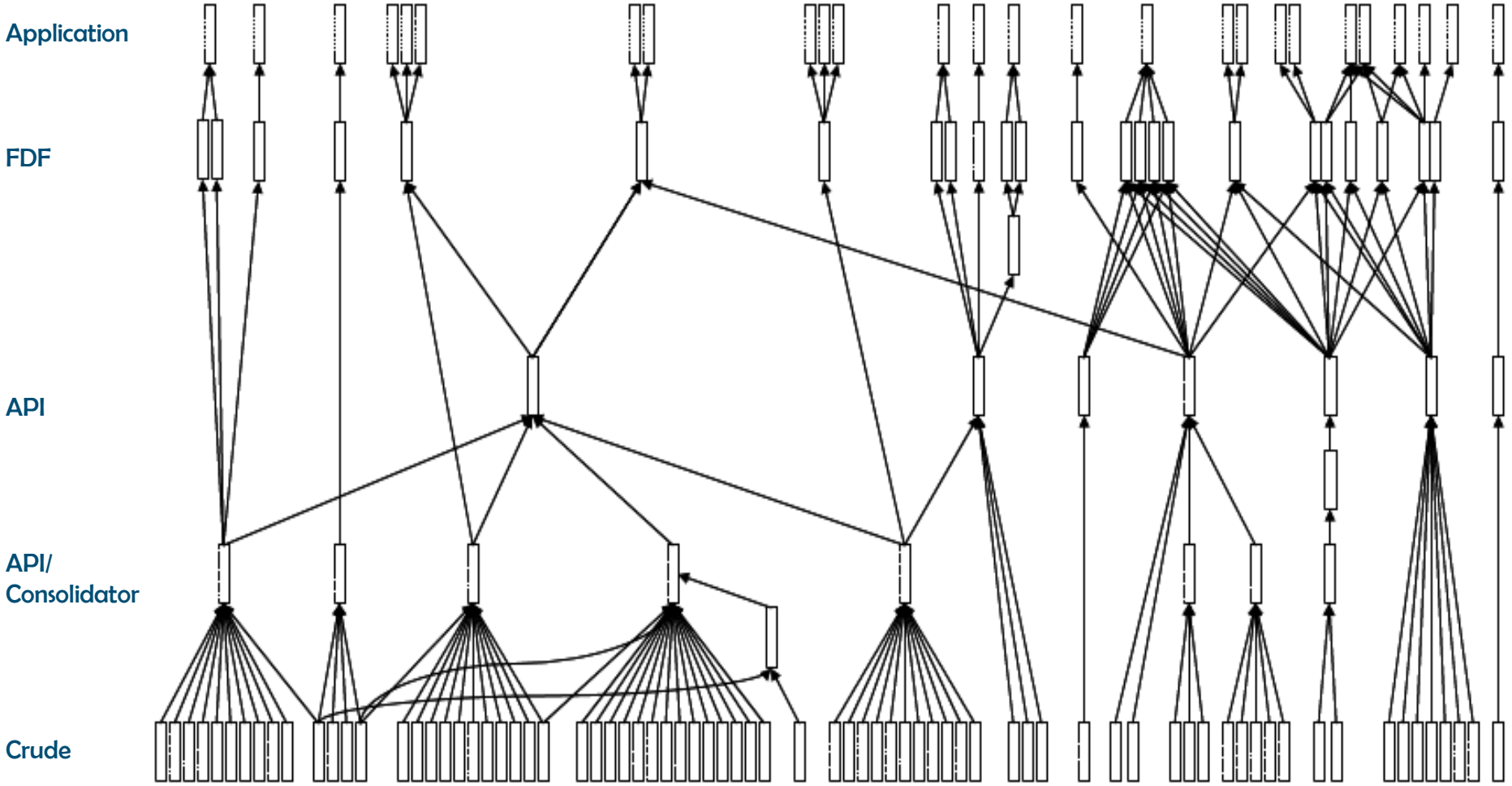
The Heparin Supply Chain



General Crude Heparin Supply Chain (China) Risks/Traceability

Intestines

Intestines

Slaughter Houses
> 25,000 (2 millions Kills/day)

Casting Workshops >1,000. Buy pigs Intestines.
Daily processing 1,000-20,000 kg intestines.
Mucosa
Crude:15-300kg/month.

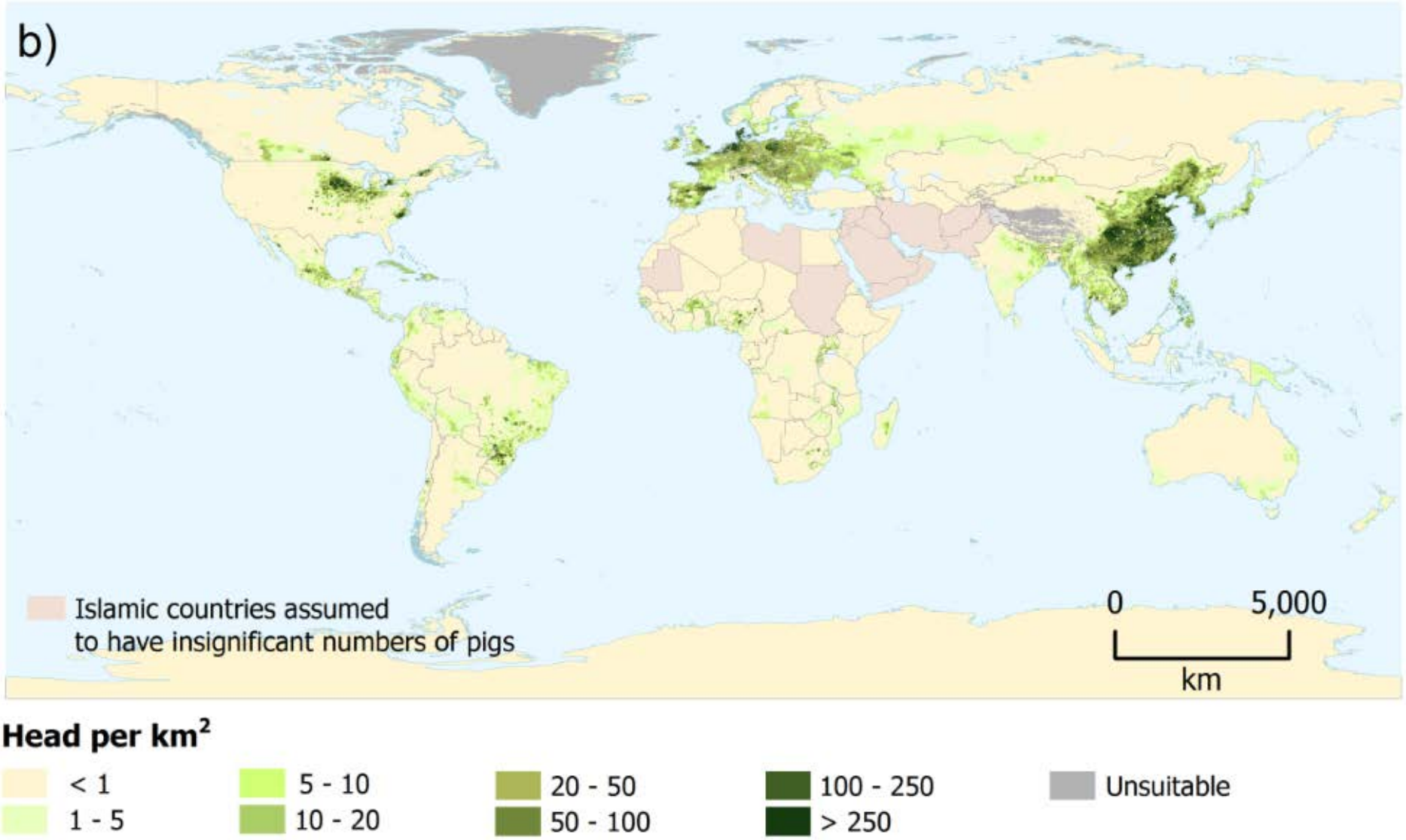
Local Brokers: Dozens. Digestion, Resin, Elute, Precip.
Crude heparin. Potency test

Consolidators: Dozens. Mix crude daily output. Dissolve.
Precip. Dry. Multiple tests 300-2,000 kg/month. Some
consolidators are also heparin pharma companies.

Foreign buyers

Domestic Pharma buyers

Global distributions of pigs



Robinson TP, Wint GRW, Conchedda G, Van Boeckel TP, Ercoli V, et al. (2014) Mapping the Global Distribution of Livestock. PLoS ONE 9(5): e96084. doi:10.1371/journal.pone.0096084
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0096084

Economically Motivated Adulteration (EMA)

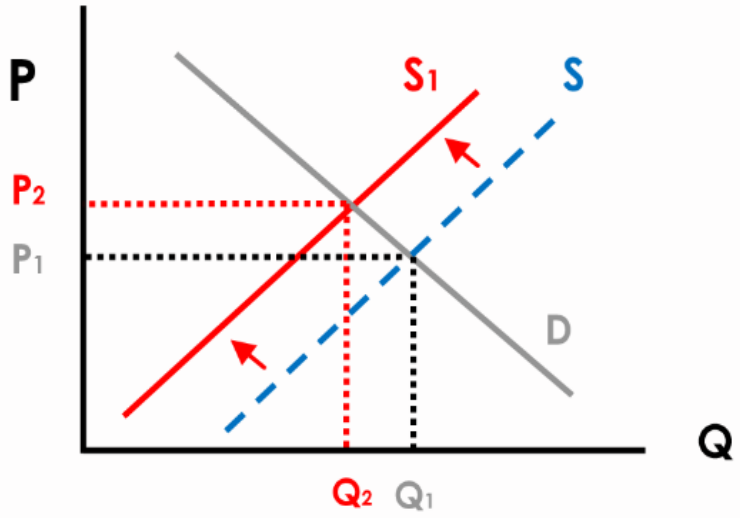
Working Definition of EMA

"For purposes of this public meeting, FDA proposes a working definition of EMA as the fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain. EMA includes dilution of products with increased quantities of an already present substance (e.g., increasing inactive ingredients of a drug with a resulting reduction in strength of the finished product, or watering down of juice) to the extent that such dilution poses a known or possible health risk to consumers, as well as the addition or substitution of substances in order to mask dilution."

Federal Register /Vol. 74, No. 64 /Monday, April 6, 2009 /Notices
Department of Health And Human Services/Food and Drug Administration
[Docket No. FDA–2009–N–0166]

https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm163619.htm

Econ 101



FALL IN SUPPLY

1. ↑P_R Price of related good
2. ↑C Cost of production
3. Unfavourable unplanned factors (i.e. severe growing conditions for crops)

KEY: The interaction of **supply** and **demand** determines the optimal **PRICE** and **QUANTITY DEMANDED** (aka **Equilibrium P** and **Q**)

https://piigsty.files.wordpress.com/2011/10/piigsty-econ-101-8-market-equilib1.png

Blue Ear Disease

Blue Ear Disease

Fatal virus that affected the pig supply in China

From the Washington Post, 9/16/2007:

"Moving rapidly from one farm to the next, the virus has been devastating pig communities throughout China for more than a year, wiping out entire herds, driving pork prices up nearly 87% in a year and helping push the country's inflation rate to its highest levels since 1996. The Chinese government has admitted that the swine deaths amount to an epidemic…"

http://www.washingtonpost.com/wp-dyn/content/article/2007/09/15/AR2007091501647.html

Effects of Blue Ear Disease

- Supply of raw material drops
- Demand for heparin stays the same
- Econ 101—price increases
- Higher price = Higher incentive for EMA
- Enter over-sulfated chondroitin sulfate (OSCS)

OSCS

Crude Heparin Pricing

Crude heparin comes in various grades

- Depends on stage of purification
- Form transported (resin/powder/liquid)
- Sophistication of crude operations
- Whether brokers/middlemen consolidate

Therefore price is a function of purity/potency

- $ = weight X potency
- Potency confirmed via various tests

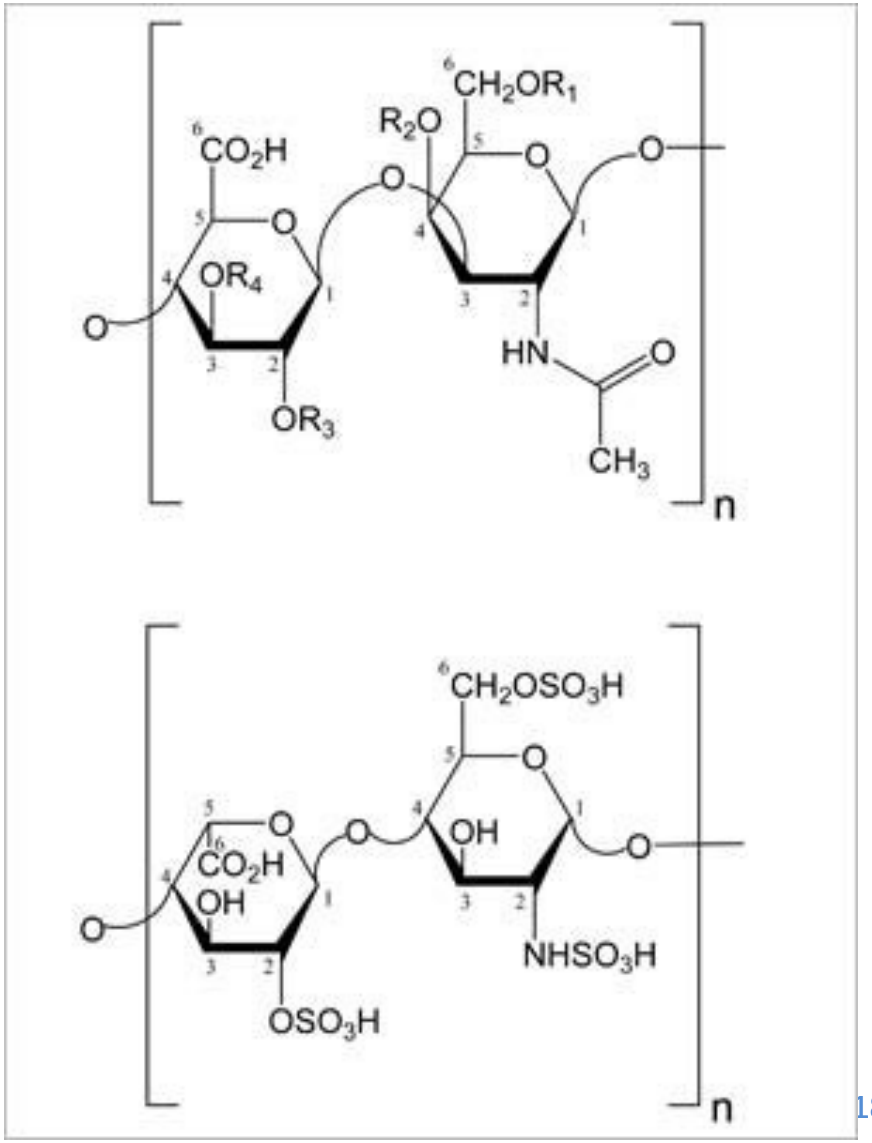
2 Options for EMA

- Increase the apparent potency => increased price
- A cheaper material with similar potency test results => reduce your cost

Heparin vs OSCS

Chondroitin Sulfate

Heparin



http://web.mit.edu/newsoffice/2008/heparin-1203.html

OSCS

"OSCS is not a natural product arising from animal sources. Therefore, it must be concluded that this was not a case of accidental contamination, but that OSCS was intentionally added to the raw heparin product as an act of purposeful adulteration."

"The high charge density of OSCS resulted in strong anti-factor IIa activity, allowing the contaminated sample lots to pass through the anticoagulation potency screens that were used to determine heparin efficacy and purity."

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3015169/

OSCS vs Heparin potency

Table 2 Effect of OSCS on activity of unfractionated heparin

Assay type	IU/mg (95% confidence limits)	
	Heparin	Heparin + 15% OSCS
EP Sheep Plasma	165.9 (160.4–171.4)	200.1 (193.7–206.5)
Anti-Xa	172.8 (169.1–176.5)	177.5 (173.7–181.3)
Anti-IIa	168.4 (154.4–182.4)	179.0 (162.9–186.1)

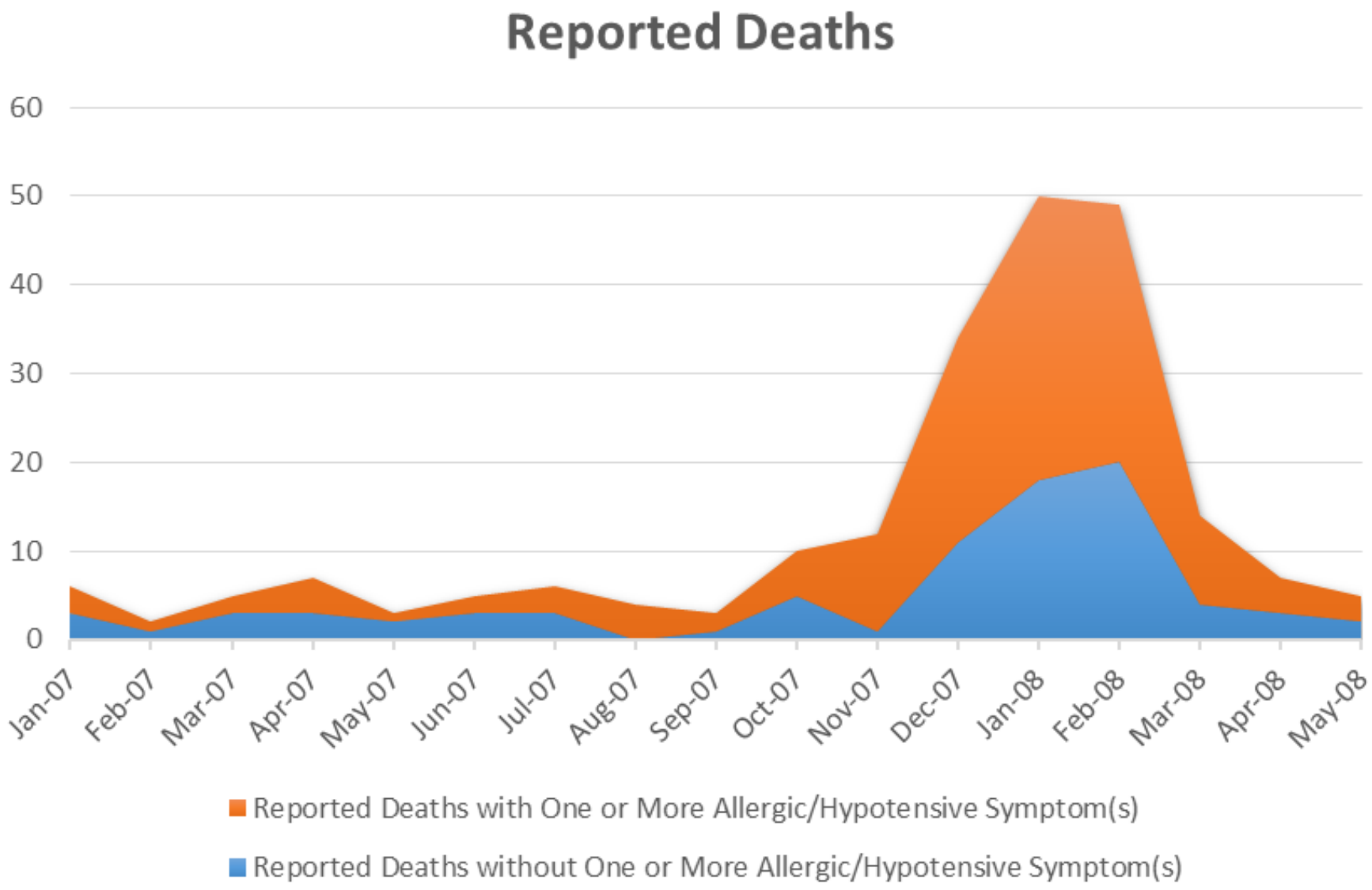
Rebecca Lever, Barbara Mulloy, Clive P. Page
Heparin – A Century of Progress, ISBN 978-3-642-23055-4
http://link.springer.com/book/10.1007%2F978-3-642-23056-1

What happened?

A Perfect Storm

- Opaque supply chain
  - Many didn't know who crude manufacturers were (bought material from brokers/consolidators)
  - Comingled materials hinder traceability
- Crude material with natural impurities
- Weak analytical controls
  - Only test for potency
  - Methods wouldn't detect OSCS
- Supply disruption causing spike in price
  - Increased incentive for OSCS contamination

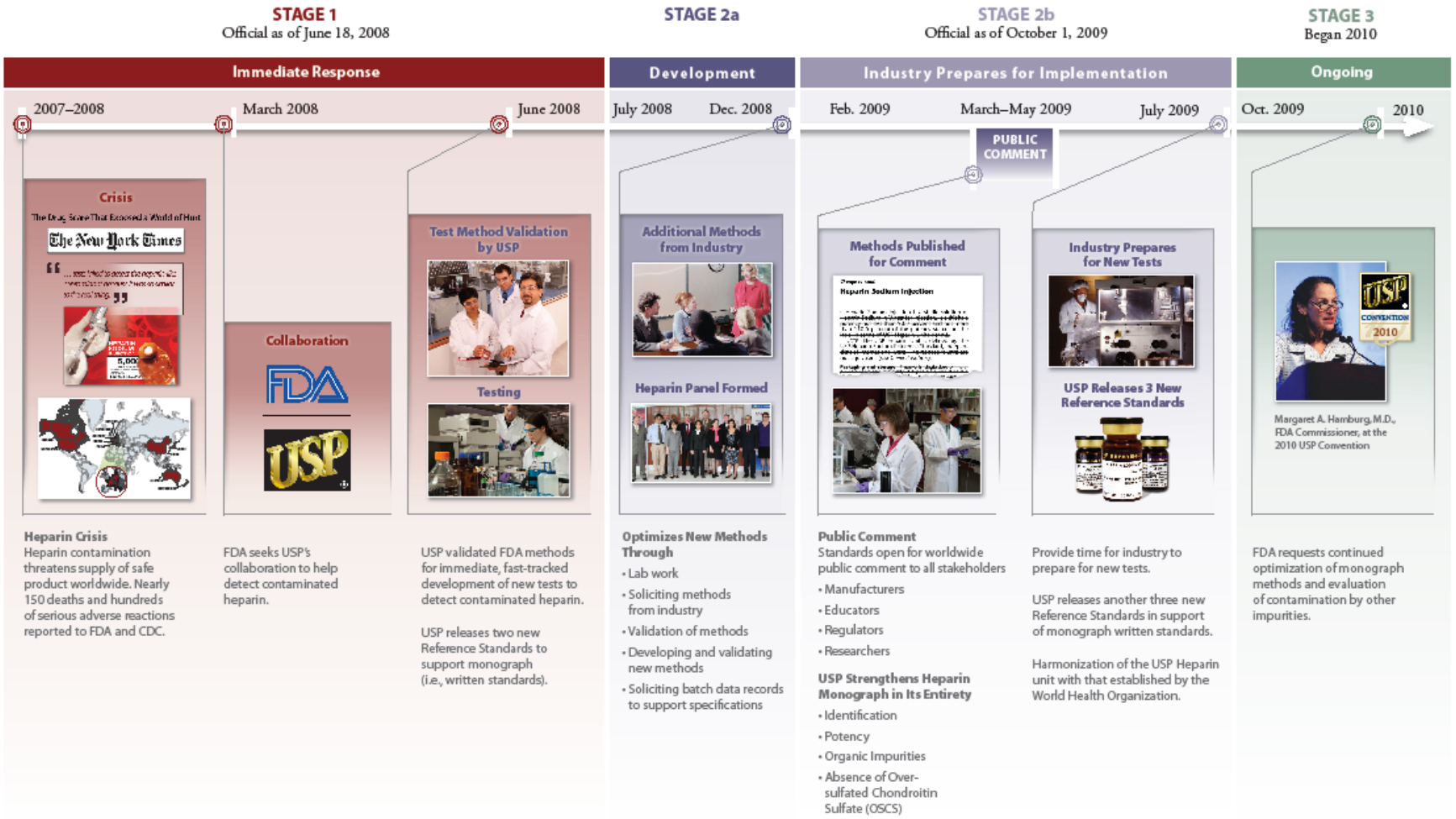
Adverse Event Trends



https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM112669

FDA and USP response

Advancing Health Through Public Standards
USP & FDA's Response to Heparin Crisis: A Timeline of Events



http://www.usp.org/sites/default/files/usp_pdf/EN/valueOfStandards/heparinTimeline.pdf

Import Alert 55-03

Implemented in February 2012

- https://www.accessdata.fda.gov/cms_ia/importalert_821.html
- Firms linked to historical OSCS contamination
- Includes firms with violative inspections (WL, etc.)
- Serves as “one stop shop” for heparin industry to be aware of firms FDA considers unacceptable

Import Alert 55-03

Pass through issue

- Material from these firms may not come across the border (internal commerce in China)
- All sponsors and API sites directly notified that use of firms on the list could result in their products being considered adulterated
- API sites committed to removing listed sites, all DMF and applications were updated accordingly

FDA Heparin Guidance

Final guidance published June 2013

Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.pdf

Recommendations to better control crude heparin that might contain over-sulfated chondroitin sulfate (OSCS) or non-porcine material (ruminant material) contaminants

Questions?